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(54) Title: COMPOUNDS, COMPOSITIONS AND TREATMENT OF ALLERGIES AND INFLAMMATION THEREWITH			
(57) Abstract			
<p>Novel cyclohexane derivatives of formula (I) are described herein. These compounds inhibit the production of Tumor Necrosis Factor and are useful in the treatment of disease states mediated or exacerbated by TNF production; they are also useful in the mediation or inhibition of enzymatic or catalytic activity of phosphodiesterase IV and are therefore useful in the treatment of disease states in need of mediation or inhibition thereof.</p>			
<p style="text-align: right;">(I)</p>			

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COMPOUNDS, COMPOSITIONS AND TREATMENT OF ALLERGIES AND INFLAMMATION THEREWITH

Field of Invention

The present invention relates to novel compounds, pharmaceutical compositions containing these compounds, and their use in treating allergic and inflammatory diseases and for inhibiting the production of Tumor Necrosis Factor (TNF).

Background of the Invention

Bronchial asthma is a complex, multifactorial disease characterized by reversible narrowing of the airway and hyperreactivity of the respiratory tract to external stimuli.

Identification of novel therapeutic agents for asthma is made difficult by the fact that multiple mediators are responsible for the development of the disease. Thus, it seems unlikely that eliminating the effects of a single mediator will have a substantial effect on all three components of chronic asthma. An alternative to the "mediator approach" is to regulate the activity of the cells responsible for the pathophysiology of the disease.

One such way is by elevating levels of cAMP (adenosine cyclic 3',5'-monophosphate). Cyclic AMP has been shown to be a second messenger mediating the biologic responses to a wide range of hormones, neurotransmitters and drugs; [Krebs Endocrinology Proceedings of the 4th International Congress Excerpta Medica, 17-29, 1973]. When the appropriate agonist binds to specific cell surface receptors, adenylate cyclase is activated, which converts Mg^{+2} -ATP to cAMP at an accelerated rate.

Cyclic AMP modulates the activity of most, if not all, of the cells that contribute to the pathophysiology of extrinsic (allergic) asthma. As such, an elevation of cAMP would produce beneficial effects including: 1) airway smooth muscle relaxation, 2) inhibition of mast cell mediator release, 3) suppression of neutrophil degranulation, 4) inhibition of basophil degranulation, and 5) inhibition of monocyte and macrophage activation. Hence, compounds that activate adenylate cyclase or inhibit phosphodiesterase should be effective in suppressing the inappropriate activation of airway smooth muscle and a wide variety of inflammatory cells. The principal cellular mechanism for the inactivation of cAMP is hydrolysis of the 3'-phosphodiester bond by one or more of a family of isozymes referred to as cyclic nucleotide phosphodiesterases (PDEs).

It has now been shown that a distinct cyclic nucleotide phosphodiesterase (PDE) isozyme, PDE IV, is responsible for cAMP breakdown in airway smooth muscle and inflammatory cells. [Torphy, "Phosphodiesterase Isozymes: Potential Targets for Novel Anti-asthmatic Agents" in New Drugs for Asthma, Barnes, ed. IBC Technical Services Ltd., 1989]. Research indicates that inhibition of this enzyme not only produces airway smooth muscle relaxation, but also suppresses degranulation of mast cells, basophils and neutrophils along with inhibiting the activation of monocytes and neutrophils. Moreover, the beneficial effects of PDE IV inhibitors are markedly potentiated when adenylate

cyclase activity of target cells is elevated by appropriate hormones or autocoids, as would be the case *in vivo*. Thus PDE IV inhibitors would be effective in the asthmatic lung, where levels of prostaglandin E₂ and prostacyclin (activators of adenylate cyclase) are elevated. Such compounds would offer a unique approach toward the pharmacotherapy of bronchial asthma and possess significant therapeutic advantages over agents currently on the market.

The compounds of this invention also inhibit the production of Tumor Necrosis Factor (TNF), a serum glycoprotein. Excessive or unregulated TNF production has been implicated in mediating or exacerbating a number of diseases including rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, gouty arthritis and other arthritic conditions; sepsis, septic shock, endotoxic shock, gram negative sepsis, toxic shock syndrome, adult respiratory distress syndrome, cerebral malaria, chronic pulmonary inflammatory disease, silicosis, pulmonary sarcoidosis, bone resorption diseases, reperfusion injury, graft vs. host reaction, allograft rejections, fever and myalgias due to infection, such as influenza, cachexia secondary to infection or malignancy, cachexia secondary to human acquired immune deficiency syndrome (AIDS), AIDS, ARC (AIDS related complex), keloid formation, scar tissue formation, Crohn's disease, ulcerative colitis, or pyresis, in addition to a number of autoimmune diseases, such as multiple sclerosis, autoimmune diabetes and systemic lupus erythematosus.

AIDS results from the infection of T lymphocytes with Human Immunodeficiency Virus (HIV). At least three types or strains of HIV have been identified, i.e., HIV-1, HIV-2 and HIV-3. As a consequence of HIV infection, T-cell-mediated immunity is impaired and infected individuals manifest severe opportunistic infections and/or unusual neoplasms. HIV entry into the T lymphocyte requires T lymphocyte activation. Viruses such as HIV-1 or HIV-2 infect T lymphocytes after T cell activation and such virus protein expression and/or replication is mediated or maintained by such T cell activation. Once an activated T lymphocyte is infected with HIV, the T lymphocyte must continue to be maintained in an activated state to permit HIV gene expression and/or HIV replication.

Cytokines, specifically TNF, are implicated in activated T-cell-mediated HIV protein expression and/or virus replication by playing a role in maintaining T lymphocyte activation. Therefore, interference with cytokine activity such as by inhibition of cytokine production, notably TNF, in an HIV-infected individual aids in limiting the maintenance of T cell activation, thereby reducing the progression of HIV infectivity to previously uninfected cells which results in a slowing or elimination of the progression of immune dysfunction caused by HIV infection. Monocytes, macrophages, and related cells, such as kupffer and glial cells, have also been implicated in maintenance of the HIV infection. These cells, like T cells, are targets for viral replication and the level of viral replication is dependent upon the activation state of the cells. [See Rosenberg *et al.*, The

Immunopathogenesis of HIV Infection, *Advances in Immunology*, Vol. 57, 1989]. Monokines, such as TNF, have been shown to activate HIV replication in monocytes and/or macrophages [See Poli *et al.*, *Proc. Natl. Acad. Sci.*, 87:782-784, 1990], therefore, inhibition of monokine production or activity aids in limiting HIV progression as stated
5 above for T cells.

TNF has also been implicated in various roles with other viral infections, such as the cytomegalovirus (CMV), influenza virus, adenovirus, and the herpes virus for similar reasons as those noted.

TNF is also associated with yeast and fungal infections. Specifically *Candida albicans* has been shown to induce TNF production *in vitro* in human monocytes and
10 natural killer cells. [See Riipi *et al.*, *Infection and Immunity*, 58(9):2750-54, 1990; and Jafari *et al.*, *Journal of Infectious Diseases*, 164:389-95, 1991. See also Wasan *et al.*, *Antimicrobial Agents and Chemotherapy*, 35,(10):2046-48, 1991; and Luke *et al.*, *Journal of Infectious Diseases*, 162:211-214, 1990].

The ability to control the adverse effects of TNF is furthered by the use of the
15 compounds which inhibit TNF in mammals who are in need of such use. There remains a need for compounds which are useful in treating TNF-mediated disease states which are exacerbated or caused by the excessive and/or unregulated production of TNF.

Summary of the Invention

This invention relates to the novel compounds of Formula (I) which are useful in
20 the mediation or inhibition of the enzymatic activity (or catalytic activity) of phosphodiesterase IV (PDE IV). The novel compounds of Formula (I) also have Tumor Necrosis Factor (TNF) inhibitory activity.

This invention also relates to the pharmaceutical compositions comprising a
25 compound of Formula (I) and a pharmaceutically acceptable carrier or diluent.

The invention also relates to a method of mediation or inhibition of the enzymatic activity (or catalytic activity) of PDE IV in mammals, including humans, which
comprises administering to a mammal in need thereof an effective amount of a compound of Formula (I), as shown below.

The invention further provides a method for the treatment of allergic and
30 inflammatory disease which comprises administering to a mammal, including humans, in need thereof, an effective amount of a compound of Formula (I). The invention also provides a method for the treatment of asthma which comprises administering to a mammal, including humans, in need thereof, an effective amount of a compound of
35 Formula (I).

This invention also relates to a method of inhibiting TNF production in a mammal, including humans, which method comprises administering to a mammal in need of such treatment, an effective TNF inhibiting amount of a compound of Formula (I). This

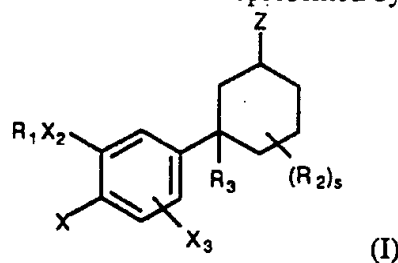
method may be used for the prophylactic treatment or prevention of certain TNF mediated disease states amenable thereto.

This invention also relates to a method of treating a human afflicted with a human immunodeficiency virus (HIV), which comprises administering to such human an effective TNF inhibiting amount of a compound of Formula (I).

The compounds of Formula (I) are also useful in the treatment of additional viral infections, where such viruses are sensitive to upregulation by TNF or will elicit TNF production *in vivo*.

The compounds of Formula (I) are also useful in the treatment of yeast and fungal infections, where such yeast and fungi are sensitive to upregulation by TNF or will elicit TNF production *in vivo*.

The novel compounds of this invention are represented by the structure:



wherein:

R_1 is $-(CR_4R_5)_nC(O)O(CR_4R_5)_mR_6$, $-(CR_4R_5)_nC(O)NR_4(CR_4R_5)_mR_6$, $-(CR_4R_5)_nO(CR_4R_5)_mR_6$, or $-(CR_4R_5)_rR_6$ wherein the alkyl moieties may be optionally substituted with one or more halogens;

m is 0 to 2;

n is 1 to 4;

r is 0 to 6;

R_4 and R_5 are independently selected from hydrogen or a C_{1-2} alkyl;

R_6 is hydrogen, methyl, hydroxyl, aryl, halo substituted aryl, aryloxy C_{1-3} alkyl, halo substituted aryloxy C_{1-3} alkyl, indanyl, indenyl, C_{7-11} polycycloalkyl, tetrahydrofuranyl, furanyl, tetrahydropyranyl, pyranal, tetrahydrothienyl, thienyl, tetrahydrothiopyranyl, thiopyranyl, C_{3-6} cycloalkyl, or a C_{4-6} cycloalkyl containing one or two unsaturated bonds, wherein the cycloalkyl and heterocyclic moieties may be optionally substituted by 1 to 3 methyl groups or one ethyl group;

provided that:

- a) when R_6 is hydroxyl, then m is 2; or
- b) when R_6 is hydroxyl, then r is 2 to 6; or
- c) when R_6 is 2-tetrahydropyranyl, 2-tetrahydrothiopyranyl, 2-tetrahydrofuranyl, or 2-tetrahydrothienyl, then m is 1 or 2; or
- d) when R_6 is 2-tetrahydropyranyl, 2-tetrahydrothiopyranyl, 2-tetrahydrofuranyl, or 2-tetrahydrothienyl, then r is 1 to 6;

- e) when n is 1 and m is 0, then R₆ is other than H in $-(\text{CR}_4\text{R}_5)_n\text{O}(\text{CR}_4\text{R}_5)_m\text{R}_6$;
 X is YR₂, halogen, nitro, NR₄R₅, or formyl amine;
 Y is O or S(O)_{m'};
 m' is a number having a value of 0, 1, or 2;
- 5 X₂ is O or NR₈;
 X₃ is hydrogen or X;
 R₂ is independently selected from -CH₃ or -CH₂CH₃ optionally substituted by 1 or more halogens;
 s is 0 to 4;
- 10 R₃ is hydrogen, halogen, C₁₋₄ alkyl, halo-substituted C₁₋₄ alkyl, CH₂NHC(O)C(O)NH₂, -CH=CR₈'R₈', cyclopropyl optionally substituted by R₈', CN, OR₈, CH₂OR₈, NR₈R₁₀, CH₂NR₈R₁₀, C(Z')H, C(O)OR₈, C(O)NR₈R₁₀, or C≡CR₈';
 Z' is O, NR₉, NOR₈, NCN, C(-CN)₂, CR₈CN, CR₈NO₂, CR₈C(O)OR₈, CR₈C(O)NR₈R₈, C(-CN)NO₂, C(-CN)C(O)OR₉, or C(-CN)C(O)NR₈R₈;
- 15 Z is OR₁₄, OR₁₅, SR₁₄, S(O)_m'R₇, S(O)₂NR₁₀R₁₄, NR₁₀R₁₄, NR₁₄C(O)R₉, NR₁₀C(Y')R₁₄, NR₁₀C(O)OR₇, NR₁₀C(Y')NR₁₀R₁₄, NR₁₀S(O)₂NR₁₀R₁₄, NR₁₀C(NCN)NR₁₀R₁₄, NR₁₀S(O)₂R₇, NR₁₀C(CR₄NO₂)NR₁₀R₁₄, NR₁₀C(NCN)SR₉, NR₁₀C(CR₄NO₂)SR₉, NR₁₀C(NR₁₀)NR₁₀R₁₄, NR₁₀C(O)C(O)NR₁₀R₁₄, or NR₁₀C(O)C(O)OR₁₄;
- 20 Y' is O or S;
 R₇ is $-(\text{CR}_4\text{R}_5)_q\text{R}_{12}$ or C₁₋₆ alkyl wherein the R₁₂ or C₁₋₆ alkyl group is optionally substituted one or more times by C₁₋₂ alkyl optionally substituted by one to three fluorines, -F, -Br, -Cl, -NO₂, -NR₁₀R₁₁, -C(O)R₈, -C(O)OR₈, -OR₈, -CN, -C(O)NR₁₀R₁₁, -OC(O)NR₁₀R₁₁, -OC(O)R₈, -NR₁₀C(O)NR₁₀R₁₁, -NR₁₀C(O)R₁₁, -NR₁₀C(O)OR₉, -NR₁₀C(O)R₁₃, -C(NR₁₀)NR₁₀R₁₁, -C(NCN)NR₁₀R₁₁, -C(NCN)SR₉, -NR₁₀C(NCN)SR₉, -NR₁₀C(NCN)NR₁₀R₁₁, -NR₁₀S(O)₂R₉, -S(O)_m'R₉, -NR₁₀C(O)C(O)NR₁₀R₁₁, -NR₁₀C(O)C(O)R₁₀, thiazolyl, imidazolyl, oxazolyl, pyrazolyl, triazolyl, or tetrazolyl;
 q is 0, 1, or 2;
- 30 R₁₂ is C₃₋₇ cycloalkyl, (2-, 3- or 4-pyridyl), pyrimidyl, pyrazolyl, (1- or 2-imidazolyl), thiazolyl, triazolyl, pyrrolyl, piperazinyl, piperidinyl, morpholinyl, furanyl, (2- or 3-thienyl), (4- or 5-thiazolyl), quinolinyl, naphthyl, or phenyl;
 R₈ is independently selected from hydrogen or R₉;
 R₈' is R₈ or fluorine;
- 35 R₉ is C₁₋₄ alkyl optionally substituted by one to three fluorines;
 R₁₀ is OR₈ or R₁₁;
 R₁₁ is hydrogen, or C₁₋₄ alkyl optionally substituted by one to three fluorines; or when R₁₀ and R₁₁ are as NR₁₀R₁₁ they may together with the nitrogen form a 5 to 7

membered ring optionally containing at least one additional heteroatom selected from O, N, or S;

R₁₃ is oxazolidinyl, oxazolyl, thiazolyl, pyrazolyl, triazolyl, tetrazolyl, imidazolyl, imidazolidinyl, thiazolidinyl, isoxazolyl, oxadiazolyl, or thiadiazolyl, and each of these
5 heterocyclic rings is connected through a carbon atom and each may be unsubstituted or substituted by one or two C₁₋₂ alkyl groups;

R₁₄ is hydrogen or R₇; or when R₁₀ and R₁₄ are as NR₁₀R₁₄ they may together with the nitrogen form a 5 to 7 membered ring optionally containing one or more additional heteroatoms selected from O, N, or S;

10 R₁₅ is C(O)R₁₄, C(O)NR₄R₁₄, S(O)₂R₇, or S(O)₂NR₄R₁₄;
provided that:

f) when X₂ is oxygen, X₃ and R₃ are hydrogen and s is 0, then R₃ is other than OH or OCH₃;

15 f) when Z is OH, X is YR₂ where Y is oxygen and R₂ is CH₃, X₂ is oxygen, X₃ is hydrogen, s is 0, and R₁ is CH₃, then R₃ is other than COOH;

g) when Z is OH, or OCH₃, X₂ is oxygen, X₃ is hydrogen, s is 0, and X is YR₂, then R₃ is other than H;

h) when Z is OS(O)₂C₁₋₆ alkyl or OS(O)₂ aryl, X₂ is oxygen, X₃ is hydrogen, s is 0, then R₃ is other than OR₈;

20 i) when R₁₂ is N-pyrazolyl, N-imidazolyl, N-triazolyl, N-pyrrolyl, N-piperaziny, N-piperidinyl, or N-morpholinyl, then q is not 1; or

j). when Z is OH or OSO₂R₇ and R₃ is CH₃, CHOH or CH₂OC₁₋₃ alkyl, then R₁X₂ is not C₁₋₃ alkoxy and X is not halogen, methoxy, ethoxy, methylthio or ethylthio;

25 k) when Z is -NH₂, NH(C₁₋₃ alkyl), N(C₁₋₃ alkyl)₂, NH(CH₂)₂₋₅C(O)Ar where Ar is naphthyl or phenyl or Z is unsubstituted or substituted pyrrolidinyl, piperidinyl, morpholinyl or piperaziny and R₃ is CH₃, CHOH or CH₂OC₁₋₃ alkyl, then R₁X₂ is not C₁₋₃ alkoxy and X is not halogen, methoxy, ethoxy, methylthio or ethylthio;
or a pharmaceutically acceptable salts thereof.

Detailed Description of the Invention

30 This invention relates to the novel compounds of Formula (I), and to pharmaceutical compositions comprising a compound of Formula (I) and a pharmaceutically acceptable carrier or diluent. This invention also relates to a method of mediating or inhibiting the enzymatic activity (or catalytic activity) of PDE IV in a mammal in need thereof and to inhibiting the production of TNF in a mammal in need
35 thereof, which comprises administering to said mammal an effective amount of a compound of Formula (I).

Phosphodiesterase IV inhibitors are useful in the treatment of a variety of allergic and inflammatory diseases including: asthma, chronic bronchitis, atopic dermatitis,

urticaria, allergic rhinitis, allergic conjunctivitis, vernal conjunctivitis, eosinophilic granuloma, psoriasis, rheumatoid arthritis, septic shock, ulcerative colitis, Crohn's disease, reperfusion injury of the myocardium and brain, chronic glomerulonephritis, endotoxic shock and adult respiratory distress syndrome. In addition, PDE IV inhibitors are useful
5 in the treatment of diabetes insipidus, [Kidney Int., 37:362, 1990; Kidney Int., 35:494, 1989] and central nervous system disorders such as depression and multi-infarct dementia.

The compounds of Formula (I) are also useful in the treatment of viral infections, where such viruses are sensitive to upregulation by TNF or will elicit TNF production *in vivo*. The viruses contemplated for treatment herein are those that produce TNF as a result
10 of infection, or those which are sensitive to inhibition, such as by decreased replication, directly or indirectly, by the TNF inhibitors of Formula (I). Such viruses include, but are not limited to HIV-1, HIV-2 and HIV-3, cytomegalovirus (CMV), influenza, adenovirus and the Herpes group of viruses, such as, but not limited to, *Herpes zoster* and *Herpes simplex*.

15 The compounds of Formula (I) are also useful in the treatment of yeast and fungal infections, where such yeast and fungi are sensitive to upregulation by TNF or will elicit TNF production *in vivo*. A preferred disease state for treatment is fungal meningitis. Additionally, the compounds of Formula (I) may be administered in conjunction with other drugs of choice for systemic yeast and fungal infections. Drugs of choice for fungal
20 infections, include but are not limited to the class of compounds called the polymyxins, such as Polymycin B, the class of compounds called the imidazoles, such as clotrimazole, econazole, miconazole, and ketoconazole; the class of compounds called the triazoles, such as fluconazole, and itranazole, and the class of compound called the Amphotericins, in particular Amphotericin B and liposomal Amphotericin B.

25 The co-administration of the anti-fungal agent with a compound of Formula (I) may be in any preferred composition for that compound such as is well known to those skilled in the art, for instance the various Amphotericin B formulations. Co-administration of an anti-fungal agent with a compound of Formula (I) may mean simultaneous administration or in practice, separate administration of the agents to the
30 mammal but in a consecutive manner. In particular, the compounds of Formula (I) may be co-administered with a formulation of Amphotericin B, notably for systemic fungal infections. The preferred organism for treatment is the *Candida* organism. The compounds of Formula (I) may be co-administered in a similar manner with anti-viral or anti-bacterial agents.

35 The compounds of Formula (I) may also be used for inhibiting and/or reducing the toxicity of an anti-fungal, anti-bacterial or anti-viral agent by administering an effective amount of a compound of Formula (I) to a mammal in need of such treatment. Preferably, a compound of Formula (I) is administered for inhibiting or reducing the toxicity of the

Amphotericin class of compounds, in particular Amphotericin B.

The preparation of a pharmaceutically acceptable salt will be determined by the nature of the compound itself, and can be prepared by conventional techniques readily available to one skilled in the art.

5 When R₁ is an alkyl substituted by 1 or more halogens, the halogens are preferably fluorine and chlorine, more preferably a C₁₋₄ alkyl substituted by 1 or more fluorines. The preferred halo-substituted alkyl chain length is one or two carbons, and most preferred are the moieties -CF₃, -CH₂F, -CHF₂, -CF₂CHF₂, -CH₂CF₃, and -CH₂CHF₂. Preferred R₁ substituents for the compounds of Formula (I) are CH₂-cyclopropyl, CH₂-
10 C₅₋₆ cycloalkyl, C₄₋₆ cycloalkyl, C₇₋₁₁ polycycloalkyl, (3- or 4-cyclopentenyl), phenyl, tetrahydrofuran-3-yl, benzyl or C₁₋₂ alkyl optionally substituted by 1 or more fluorines, -(CH₂)₁₋₃C(O)O(CH₂)₀₋₂CH₃, -(CH₂)₁₋₃O(CH₂)₀₋₂CH₃, and -(CH₂)₂₋₄OH.

When R₁ term contains the moiety (CR₄R₅), the R₄ and R₅ terms are independently hydrogen or alkyl. This allows for branching of the individual methylene
15 units as (CR₄R₅)_n or (CR₄R₅)_m; each repeating methylene unit is independent of the other, e.g., (CR₄R₅)_n wherein n is 2 can be -CH₂CH(-CH₃)-, for instance. The individual hydrogen atoms of the repeating methylene unit or the branching hydrocarbon can optionally be substituted by fluorine independent of each other to yield, for instance, the preferred R₁ substitutions, as noted above.

20 When R₁ is a C₇₋₁₁ polycycloalkyl, examples are bicyclo[2.2.1]-heptyl, bicyclo[2.2.2]octyl, bicyclo[3.2.1]octyl, tricyclo[5.2.1.0^{2,6}]decyl, etc. additional examples of which are described in Saccamano *et al.*, WO 87/06576, published 5 November 1987, whose disclosure is incorporated herein by reference in its entirety.

Z is preferably OR₁₄, OR₁₅, SR₁₄, S(O)_mR₇, S(O)₂NR₁₀R₁₄, NR₁₀R₁₄,
25 NR₁₄C(O)R₉, NR₁₀C(O)R₁₄, NR₁₀C(O)OR₇, NR₁₀C(O)NR₁₀R₁₄, NR₁₀S(O)₂NR₁₀R₁₄, NR₁₀C(NCN)NR₁₀R₁₄, NR₁₀S(O)₂R₇, NR₁₀C(CR₄NO₂)NR₁₀R₁₄, NR₁₀C(NCN)SR₉, NR₁₀C(CR₄NO₂)SR₉, NR₁₀C(NR₁₀)NR₁₀R₁₄, NR₁₀C(O)C(O)NR₁₀R₁₄, or NR₁₀C(O)C(O)OR₁₄; most preferred are those compounds wherein the R₁₄ group of Z is R₄.

30 Preferred X groups for Formula (I) are those wherein X is YR₂ and Y is oxygen. The preferred X₂ group for Formula (I) is that wherein X₂ is oxygen. The preferred X₃ group for Formula (I) is that wherein X₃ is hydrogen. Preferred R₂ groups, where applicable, is a C₁₋₂ alkyl optionally substituted by 1 or more halogens. The halogen atoms are preferably fluorine and chlorine, more preferably fluorine. More preferred R₂
35 groups are those wherein R₂ is methyl, or the fluoro-substituted alkyls, specifically a C₁₋₂ alkyl, such as a -CF₃, -CHF₂, or -CH₂CHF₂ moiety. Most preferred are the -CHF₂ and -CH₃ moieties.

Preferred R₃ moieties are C(O)NH₂, CH₂NHC(O)C(O)NH₂, C≡CR₈, CN,

C(Z')H, CH₂OH, CH₂F, CF₂H, and CF₃. More preferred are C≡CH and CN. Z' is preferably O or NOR₈.

Preferred R₇ moieties include optionally substituted -(CH₂)₁₋₂(cyclopropyl), -(CH₂)₀₋₂(cyclobutyl), -(CH₂)₀₋₂(cyclopentyl), -(CH₂)₀₋₂(cyclohexyl), -(CH₂)₀₋₂(2-, 3- or 4-pyridyl), (CH₂)₁₋₂(2-imidazolyl), (CH₂)₂(4-morpholinyl), (CH₂)₂(4-piperazinyl), (CH₂)₁₋₂(2-thienyl), (CH₂)₁₋₂(4-thiazolyl), and (CH₂)₀₋₂phenyl;

Preferred rings when R₁₀ and R₁₁ in the moiety -NR₁₀R₁₁ together with the nitrogen to which they are attached form a 5 to 7 membered ring optionally containing at least one additional heteroatom selected from O, N, or S include, but are not limited to 1-imidazolyl, 2-(R₈)-1-imidazolyl, 1-pyrazolyl, 3-(R₈)-1-pyrazolyl, 1-triazolyl, 2-triazolyl, 5-(R₈)-1-triazolyl, 5-(R₈)-2-triazolyl, 5-(R₈)-1-tetrazolyl, 5-(R₈)-2-tetrazolyl, 1-tetrazolyl, 2-tetrazolyl, morpholinyl, piperazinyl, 4-(R₈)-1-piperazinyl, or pyrrolyl ring.

Preferred rings when R₁₀ and R₁₄ in the moiety -NR₁₀R₁₄ together with the nitrogen to which they are attached may form a 5 to 7 membered ring optionally containing at least one additional heteroatom selected from O, N, or S include, but are not limited to 1-imidazolyl, 1-pyrazolyl, 1-triazolyl, 2-triazolyl, 1-tetrazolyl, 2-tetrazolyl, morpholinyl, piperazinyl, and pyrrolyl. The respective rings may be additionally substituted, where applicable, on an available nitrogen or carbon by the moiety R₇ as described herein for Formula (I). Illustrations of such carbon substitutions includes, but is not limited to, 2-(R₇)-1-imidazolyl, 4-(R₇)-1-imidazolyl, 5-(R₇)-1-imidazolyl, 3-(R₇)-1-pyrazolyl, 4-(R₇)-1-pyrazolyl, 5-(R₇)-1-pyrazolyl, 4-(R₇)-2-triazolyl, 5-(R₇)-2-triazolyl, 4-(R₇)-1-triazolyl, 5-(R₇)-1-triazolyl, 5-(R₇)-1-tetrazolyl, and 5-(R₇)-2-tetrazolyl. Applicable nitrogen substitution by R₇ includes, but is not limited to, 1-(R₇)-2-tetrazolyl, 2-(R₇)-1-tetrazolyl, 4-(R₇)-1-piperazinyl. Where applicable, the ring may be substituted one or more times by R₇.

Preferred groups for NR₁₀R₁₄ which contain a heterocyclic ring are 5-(R₁₄)-1-tetrazolyl, 2-(R₁₄)-1-imidazolyl, 5-(R₁₄)-2-tetrazolyl, 4-(R₁₄)-1-piperazinyl, or 4-(R₁₅)-1-piperazinyl.

Preferred rings for R₁₃ include (2-, 4- or 5-imidazolyl), (3-, 4- or 5-pyrazolyl), (4- or 5-triazolyl[1,2,3]), (3- or 5-triazolyl[1,2,4]), (5-tetrazolyl), (2-, 4- or 5-oxazolyl), (3-, 4- or 5-isoxazolyl), (3- or 5-oxadiazolyl[1,2,4]), (2-oxadiazolyl[1,3,4]), (2-thiadiazolyl[1,3,4]), (2-, 4-, or 5-thiazolyl), (2-, 4-, or 5-oxazolidinyl), (2-, 4-, or 5-thiazolidinyl), or (2-, 4-, or 5-imidazolidinyl).

When the R₇ group is optionally substituted by a heterocyclic ring such as imidazolyl, pyrazolyl, triazolyl, tetrazolyl, or thiazolyl, the heterocyclic ring itself may be optionally substituted by R₈ either on an available nitrogen or carbon atom, such as 1-(R₈)-2-imidazolyl, 1-(R₈)-4-imidazolyl, 1-(R₈)-5-imidazolyl, 1-(R₈)-3-pyrazolyl, 1-(R₈)-4-pyrazolyl, 1-(R₈)-5-pyrazolyl, 1-(R₈)-4-triazolyl, or 1-(R₈)-5-triazolyl. Where

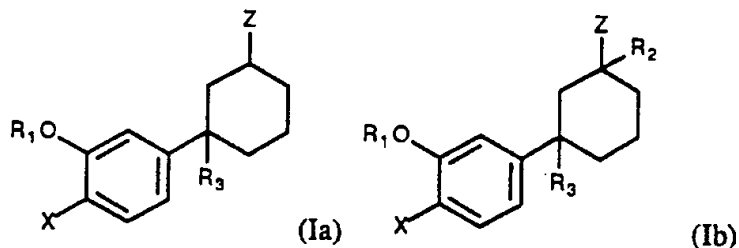
applicable, the ring may be substituted one or more times by R₈.

- Preferred are those compounds of Formula (I) wherein R₁ is -CH₂-cyclopropyl, -CH₂-C₅₋₆ cycloalkyl, -C₄₋₆ cycloalkyl, tetrahydrofuran-3-yl, (3- or 4-cyclopentenyl), benzyl or -C₁₋₂ alkyl optionally substituted by 1 or more fluorines, and -(CH₂)₂₋₄ OH;
- 5 R₂ is methyl or fluoro-substituted alkyl, R₃ is CN or C≡CR₈; and X is YR₂.

Most preferred are those compounds wherein R₁ is -CH₂-cyclopropyl, cyclopentyl, methyl or CF₂H; R₃ is CN or C≡CH; X is YR₂; Y is oxygen; X₂ is oxygen; X₃ is hydrogen; and R₂ is CF₂H or methyl.

A preferred subgenus of Formula (I) is the compounds of Formula (Ia) and (Ib)

10



wherein:

- R₁ is -CH₂-cyclopropyl, -CH₂-C₅₋₆ cycloalkyl, -C₄₋₆ cycloalkyl, C₇₋₁₁ polycycloalkyl, (3- or 4-cyclopentenyl), phenyl, tetrahydrofuran-3-yl, benzyl or C₁₋₂ alkyl optionally substituted by 1 or more fluorines, -(CH₂)₁₋₃C(O)O(CH₂)₀₋₂CH₃,
 15 -(CH₂)₁₋₃O(CH₂)₀₋₂CH₃, and -(CH₂)₂₋₄OH;

m is 0 to 2;

n is 1 to 4;

r is 0 to 6;

- 20 R₄ and R₅ are independently selected from hydrogen or a C₁₋₂ alkyl;

- R₆ is hydrogen, methyl, hydroxyl, aryl, halo substituted aryl, aryloxyC₁₋₃ alkyl, halo substituted aryloxyC₁₋₃ alkyl, indanyl, indenyl, C₇₋₁₁ polycycloalkyl, tetrahydrofuranyl, furanyl, tetrahydropyranyl, pyranal, tetrahydrothienyl, thienyl, tetrahydrothiopyranal, thiopyranal, C₃₋₆ cycloalkyl, or a C₄₋₆ cycloalkyl containing one
 25 or two unsaturated bonds, wherein the cycloalkyl and heterocyclic moieties may be optionally substituted by 1 to 3 methyl groups or one ethyl group;

provided that:

- a) when R₆ is hydroxyl, then m is 2; or
 b) when R₆ is hydroxyl, then r is 2 to 6; or
 30 c) when R₆ is 2-tetrahydropyranyl, 2-tetrahydrothiopyranal, 2-tetrahydrofuranyl, or 2-tetrahydrothienyl, then m is 1 or 2; or
 d) when R₆ is 2-tetrahydropyranyl, 2-tetrahydrothiopyranal, 2-tetrahydrofuranyl, or 2-tetrahydrothienyl, then r is 1 to 6;
 e) when n is 1 and m is 0, then R₆ is other than H in -(CR₄R₅)_nO(CR₄R₅)_mR₆;

X is YR₂, halogen, nitro, NR₄R₅, or formyl amine;

Y is O or S(O)_{m'};

m' is 0, 1, or 2;

R₂ is -CH₃ or -CH₂CH₃ optionally substituted by 1 or more halogens;

5 R₃ is hydrogen, C₁₋₄ alkyl, CH₂NHC(O)C(O)NH₂, halo-substituted C₁₋₄ alkyl, CN, CH₂OR₈, C(Z')H, C(O)OR₈, C(O)NR₈R₁₀, or C≡CR₈;

Z' is O or NOR₈;

Z is OR₁₄, OR₁₅, SR₁₄, S(O)_{m'}R₇, S(O)₂NR₁₀R₁₄, NR₁₀R₁₄, NR₁₄C(O)R₉,
NR₁₀C(O)R₁₄, NR₁₀C(O)OR₇, NR₁₀C(O)NR₁₀R₁₄, NR₁₀S(O)₂NR₁₀R₁₄,
10 NR₁₀C(NCN)NR₁₀R₁₄, NR₁₀S(O)₂R₇, NR₁₀C(CR₄NO₂)NR₁₀R₁₄,
NR₁₀C(NCN)SR₉, NR₁₀C(CR₄NO₂)SR₉, NR₁₀C(NR₁₀)NR₁₀R₁₄,
NR₁₀C(O)C(O)NR₁₀R₁₄, or NR₁₀C(O)C(O)OR₁₄;

R₇ is -(CR₄R₅)_qR₁₂ or C₁₋₆ alkyl wherein the R₁₂ or C₁₋₆ alkyl group is
optionally substituted one or more times by C₁₋₂ alkyl optionally substituted by one to
15 three fluorines, -F, -Br, -Cl, -NO₂, -NR₁₀R₁₁, -C(O)R₈, -C(O)OR₈, -OR₈, -CN, -
C(O)NR₁₀R₁₁, -OC(O)NR₁₀R₁₁, -OC(O)R₈, -NR₁₀C(O)NR₁₀R₁₁, -NR₁₀C(O)R₁₁,
-NR₁₀C(O)OR₉, -NR₁₀C(O)R₁₃, -C(NR₁₀)NR₁₀R₁₁, -C(NCN)NR₁₀R₁₁, -
C(NCN)SR₉, -NR₁₀C(NCN)SR₉, -NR₁₀C(NCN)NR₁₀R₁₁, -NR₁₀S(O)₂R₉,
-S(O)_{m'}R₉, -NR₁₀C(O)C(O)NR₁₀R₁₁, -NR₁₀C(O)C(O)R₁₀, thiazolyl, imidazolyl,
20 oxazolyl, pyrazolyl, triazolyl, or tetrazolyl;

q is 0, 1, or 2;

R₁₂ is C₃₋₇ cycloalkyl, (2-, 3- or 4-pyridyl), (1- or 2-imidazolyl), piperazinyl,
morpholinyl, (2- or 3-thienyl), (4- or 5-thiazolyl), or phenyl;

R₈ is independently selected from hydrogen or R₉;

25 R₉ is C₁₋₄ alkyl optionally substituted by one to three fluorines;

R₁₀ is OR₈ or R₁₁;

R₁₁ is hydrogen or C₁₋₄ alkyl optionally substituted by one to three fluorines; or
when R₁₀ and R₁₁ are as NR₁₀R₁₁ they may together with the nitrogen form a 5 to 7
membered ring optionally containing at least one additional heteroatom selected from O,
30 N, or S;

R₁₃ is oxazolidinyl, oxazolyl, thiazolyl, pyrazolyl, triazolyl, tetrazolyl, imidazolyl,
imidazolidinyl, thiazolidinyl, isoxazolyl, oxadiazolyl, or thiadiazolyl, and each of these
heterocyclic rings is connected through a carbon atom and each may be unsubstituted or
substituted by one or two C₁₋₂ alkyl groups;

35 R₁₄ is hydrogen or R₇; or when R₁₀ and R₁₄ are as NR₁₀R₁₄ they may together
with the nitrogen form a 5 to 7 membered ring optionally containing one or more
additional heteroatoms selected from O, N, or S;

R₁₅ is C(O)R₁₄, C(O)NR₄R₁₄, S(O)₂R₇, or S(O)₂NR₄R₁₄;

provided that:

- f) when R₃ is hydrogen in Formula (Ia), then R₃ is other than OH or OCH₃;
 - f) when Z is OH, X is YR₂ where Y is oxygen and R₂ is CH₃, X₂ is oxygen, X₃ is hydrogen, s is 0, R₂ is CH₃ in YR₂, and R₁ is CH₃, then R₃ is other than COOH;
 - 5 g) when Z is OH, or OCH₃, X₂ is oxygen, X₃ is hydrogen, s is 0, and X is YR₂, then R₃ is other than H;
 - h) when Z is S(O)₂C₁₋₆ alkyl or S(O)₂ aryl, X₂ is oxygen, X₃ is hydrogen, s is 0, then R₃ is other than OR₈;
 - i) when R₁₂ is N-pyrazolyl, N-imidazolyl, N-triazolyl, N-pyrrolyl, N-piperazinyl,
 - 10 N-piperidinyl, or N-morpholinyl, then q is not 1;
 - or a pharmaceutically acceptable salts thereof.
- Exemplified compounds of Formula (I) are:
- cis*-[N-methoxycarbonyl-3-cyano-3-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexyl-1-amine];
 - 15 *trans*-[N-methoxycarbonyl-3-cyano-3-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexyl-1-amine];
 - cis*-[N-methyl-N-methoxycarbonyl-3-cyano-3-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexyl-1-amine];
 - cis*-[N-methyl-1-acetamido-3-cyano-3-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexane];
 - 20 *cis*-[N-methyl-3-cyano-3-(3-cyclopentyloxy-4-methoxyphenyl)-cyclohexyl-1-amine];
 - cis*-[N-*tert*-butoxycarbonyl-N-methyl-3-cyano-3-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexyl-1-amine];
 - 25 *trans*-[1-acetamido-3-cyano-3-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexane];
 - cis*-[1-acetamido-3-cyano-3-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexane];
 - trans*-[3-cyano-3-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexyl-1-amine, hydrochloride salt];
 - cis*-3-cyano-3-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexyl-1-amine, hydrochloride salt];
 - 30 *cis*-[1-*tert*-butoxycarbonylamino-3-cyano-3-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexane]
 - b) *trans*-[1-*tert*-butoxycarbonylamino-3-cyano-3-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexane]; and
 - 35 *cis*- and *trans*-[3-cyano-3-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexan-1-ol]. It will be recognized that some of the compounds of Formula (I) may exist in both racemic and optically active forms; some may also exist in distinct diastereomeric forms possessing distinct physical and biological properties. All of these compounds are

considered to be within the scope of the present invention. Therefore another aspect of the present invention is the administration of either a racemate, a single enantiomeric form, a single diastereomeric form, or mixtures thereof.

5 The terms *cis* and *trans* denote stereochemistry at the C-1 position of the cyclohexane ring relative to the R₃ group at the C-4 position.

The term "C₁₋₃ alkyl", "C₁₋₄ alkyl", "C₁₋₆ alkyl" or "alkyl" includes both straight or branched chain radicals of 1 to 10, unless the chain length is limited thereto, including, but not limited to methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, *tert*-butyl.

10 "Alkenyl" includes both straight or branched chain radicals of 1 to 6 carbon lengths, unless the chain length is limited thereto, including but not limited to vinyl, 1-propenyl, 2-propenyl, 2-propynyl, or 3-methyl-2-propenyl.

The term "cycloalkyl" or "cycloalkyl alkyl" includes 3-7 carbon atoms, such as cyclopropyl, cyclopropylmethyl, cyclopentyl, or cyclohexyl.

15 "Aryl" or "aralkyl", unless specified otherwise, means an aromatic ring or ring system of 6-10 carbon atoms, such as phenyl, benzyl, phenethyl, or naphthyl. Preferably the aryl is monocyclic, i.e., phenyl. The alkyl chain includes both straight or branched chain radicals of 1 to 4 carbon atoms.

"Heteroaryl" means an aromatic ring system containing one or more heteroatoms, 20 such as imidazolyl, triazolyl, oxazolyl, pyridyl, pyrimidyl, pyrazolyl, pyrrolyl, furanyl, or thienyl.

"Halo" means chloro, fluoro, bromo, or iodo.

The term "inhibiting the production of IL-1" or "inhibiting the production of TNF" means:

25 a) a decrease of excessive *in vivo* IL-1 or TNF levels, respectively, in a human to normal levels or below normal levels by inhibition of the *in vivo* release of IL-1 by all cells, including but not limited to monocytes or macrophages;

b) a down regulation, at the translational or transcriptional level, of excessive *in vivo* IL-1 or TNF levels, respectively, in a human to normal levels or below normal 30 levels; or

c) a down regulation, by inhibition of the direct synthesis of IL-1 or TNF levels as a postranslational event.

The phrase "TNF mediated disease or disease states" means any and all disease states in which TNF plays a role, either by production of TNF itself, or by TNF causing 35 another cytokine to be released, such as but not limited to IL-1 or IL-6. A disease state in which IL-1, for instance is a major component, and whose production or action, is exacerbated or secreted in response to TNF, would therefore be considered a disease state mediated by TNF. As TNF- β (also known as lymphotoxin) has close structural homology

with TNF- α (also known as cachectin), and since each induces similar biologic responses and binds to the same cellular receptor, both TNF- α and TNF- β are inhibited by the compounds of the present invention and thus are herein referred to collectively as "TNF" unless specifically delineated otherwise. Preferably TNF- α is inhibited.

5 "Cytokine" means any secreted polypeptide that affects the functions of cells, and is a molecule which modulates interactions between cells in immune, inflammatory, or hematopoietic responses.

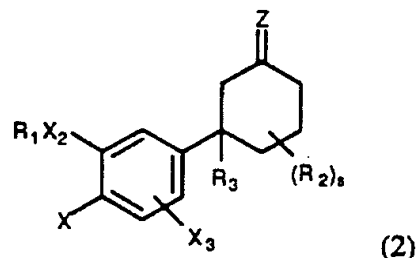
The cytokine inhibited by the present invention for use in the treatment of a HIV-infected human must be a cytokine which is implicated in (a) the initiation and/or
10 maintenance of T cell activation and/or activated T cell-mediated HIV gene expression and/or replication, and/or (b) any cytokine-mediated disease associated problem such as cachexia or muscle degeneration. Preferably this cytokine is TNF- α .

All of the compounds of Formula (I) are useful in the method of inhibiting the production of TNF, preferably by macrophages, monocytes or macrophages and
15 monocytes, in a mammal, including humans, in need thereof. All of the compounds of Formula (I) are useful in the method of inhibiting or mediating the enzymatic or catalytic activity of PDE IV and in treatment of disease states mediated thereby.

METHODS OF PREPARATION:

Preparing compounds of Formula (I) can be carried out by one of skill in the art
20 according to the procedures outlined in the Examples, *infra*. The preparation of any remaining compounds of Formula (I) not described therein may be prepared by the analogous processes disclosed herein which comprise:

a) for compounds wherein X or X₃ is other than Br, I, NO₂, amino, or S(O)_mR₂ when m' is 0, 1 or 2 and R₃ is other than C(=Z')H and wherein Z is OH, reacting a
25 compound of Formula (2)



wherein R₁ represents R₁ as defined in relation to Formula (I) or a group convertible to R₁ and X and X₃ represent X and X₃ as defined in relation to Formula (I) or a group convertible to X or X₃ and R₃ represents R₃ as defined in relation to Formula
30 (I) or a group convertible to R₃, with a suitable reducing agent, such as lithium borohydride, diisiamylborane, lithium aluminum *tris*-(*t*-butoxide), or sodium borohydride, in a suitable non-reacting solvent, such as 1,2-dimethoxyethane, tetrahydrofuran or an alcohol, to provide compounds of Formula (I) wherein R₃ is other than C(=Z')H and

wherein Z is OH; preparation of such compounds of Formula (I) wherein R₃ is C(=Z')H proceed in an analogous fashion from the compound of Formula (2) wherein =Z' is an aldehyde protecting group, such as a dimethylacetal or a dioxolane, followed by deprotection to the aldehyde and subsequent elaboration by standard procedures known to those of skill in the art to the remaining compounds of Formula (I) wherein Z' is other than O.

For compounds wherein R₃ is other than C(=Z')H and wherein Z is NH₂, NHCH₃, or N(CH₃)₂, reacting a compound of Formula (2) wherein R₁ represents R₁ as defined in relation to Formula (I) or a group convertible to R₁ and X and X₃ represent X and X₃ as defined in relation to Formula (I) or a group convertible to X or X₃ and R₃ represents R₃ as defined in relation to Formula (I) or a group convertible to R₃, with an ammonium salt, such as, for example, ammonium formate, methylamine hydrochloride, or dimethylamine hydrochloride, respectively, in the presence of a suitable reducing agent, such as sodium cyanoborohydride, in a suitable solvent, such as an alcohol, to provide compounds of Formula (I) wherein Z is NH₂, NHCH₃, or N(CH₃)₂, respectively; preparation of such compounds of Formula (I) wherein R₃ is C(=Z')H proceed in an analogous fashion from the compound of Formula (2) wherein =Z' is an aldehyde protecting group, such as a dimethylacetal or a dioxolane, followed by deprotection to the aldehyde and subsequent elaboration by standard procedures known to those of skill in the art to the remaining compounds of Formula (I) wherein Z' is other than O.

Alternatively, compounds of Formula (I) wherein Z is NH₂ may be prepared by reacting an appropriate alcohol of Formula (2) wherein Z is OH, R₁ represents R₁ as defined in relation to Formula (I) or a group convertible to R₁ and X and X₃ represent X and X₃ as defined in relation to Formula (I) or a group convertible to X or X₃ and R₃ represents R₃ as defined in relation to Formula (I) or a group convertible to R₃, with a complex of a phosphine, such as triphenyl phosphine, and an azodicarboxylate ester in the presence of an imide, such as phthalimide, followed by, e.g., hydrazinolysis in an alcoholic solvent.

Compounds of Formula (I) wherein Z is SR₁₄ may be prepared by reacting an appropriate compound of Formula (2) wherein Z is a leaving group, e.g., a mesylate, tosylate, chloride, or bromide, R₁ represents R₁ as defined in relation to Formula (I) or a group convertible to R₁ and X and X₃ represent X and X₃ as defined in relation to Formula (I) or a group convertible to X or X₃ and R₃ represents R₃ as defined in relation to Formula (I) or a group convertible to R₃, with a metal salt of a mercaptan, such as NaSR₁₄ in an appropriate aprotic solvent. Compounds of Formula (I) wherein Z is SH may be prepared by reacting an appropriate alcohol of Formula (2) wherein Z is OH with a complex of a phosphine, such as triphenyl phosphine, and an azodicarboxylate ester in the presence of thiolacetic acid, followed by hydrolysis of the resulting thiolacetate.

Compounds of Formula (I) wherein Z is OH may be interconverted using the standard alcohol inversion procedures known in the art. It will be recognized that compounds of Formula (I) may exist in two distinct diastereomeric forms possessing distinct physical and biological properties; such isomers may be separated by standard chromatographic methods. Such isomers may be independently converted to the remaining compounds of Formula (I) wherein Z is other than OH, SH, and NH₂ by any of the wide variety of O, S, and N alkylation, sulfamidation, imidation, oxidation, or acylation procedures known to those of skill in the art.

For example, with proper manipulation of any chemically sensitive functional groups, compounds of Formula (1) wherein NR₁₃R₁₄ represent a ring, such as a 1- or 2-tetrazole, may be derived from reaction of an appropriate compound of Formula (I) wherein Z is a leaving group, e.g., a mesylate, tosylate, chloride or bromide, with the appropriate metal salt of HNR₁₃R₁₄, e.g., 5-(R₁₄)-tetrazole; the appropriate compound of Formula (I) wherein Z is mesylate, tosylate, Br or Cl, derived in turn from the appropriate compound of Formula (1) wherein Z is OH.

With proper manipulation (protection/deprotection) of any chemically sensitive functional groups:

a) Compounds of the Formula (I) wherein X or X₃ are formyl amine may be formed at the last step, by formylating a compound wherein X or X₃ is NH₂, obtained by removal of a protecting group from the amine functionality; such protective groups are well known to those skilled in the art, See Greene, T. and Wuts, P.G.M., Protecting Groups in Organic Synthesis, 2nd Ed., John Wiley and Sons, New York (1991).

b) Compounds of the Formula (I) wherein X or X₃ are Br, I or SR₂ may be prepared from a similarly deprotected amine by diazotization of the amine and diazonium displacement.

c) Compounds of the Formula (I) wherein X or X₃ are NO₂ may be prepared from a similarly deprotected amine by oxidation of the amine to the nitro group.

d) Compounds of the Formula (I) wherein Y is S(O)m' when m' is 0, 1 or 2 may be prepared from the compounds of the Formula (I) wherein Y is S by oxidation of the SR₂ moiety under conditions well known those skilled in the art

It will be recognized that compounds of the Formula (I) may exist in two distinct diastereomeric forms possessing distinct physical and biological properties; such isomers may be separated by standard chromatographic methods.

Compounds of Formula (2) may be prepared in turn by the processes described in co-pending U.S. patent application number 08/130215 filed 01 October 1993.

The following sets of examples are provided to illustrate how to make and use this invention. They are not intended to limit the scope of the invention but are given for illustration purposes only.

SYNTHETIC EXAMPLES

Example 1

Preparation of *cis*- and *trans*-[3-cyano-3-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexan-1-ol]

5 Sodium cyanoborohydride (0.02 g, 0.32 mmol) was added to a solution of 3-cyano-3-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexan-1-one (0.1g, 0.32 mmol, prepared as described in co-pending U.S. patent application number 08/130215 filed 01 October 1993, and a crystal of methyl orange indicator in methanol (2 mL). Hydrogen chloride-saturated methanol was added dropwise to maintain a red color. After 2 h, the
10 reaction was treated with water and extracted three times with ether, the extract was dried (MgSO₄), was filtered and was evaporated. The crude mixture was purified by flash chromatography, eluting with 3:7 ethyl acetate/hexanes, to afford the *cis*-isomer as a colorless oil. Anal. (C₁₉H₂₃NO₃·1.125 H₂O) calcd: C, 68.39; H, 7.63; N, 4.20; found: C, 68.33; H, 7.43; N, 3.93.

15 Also isolated was the *trans*-isomer as a colorless oil. ¹H-NMR (400 MHz, CDCl₃) δ 6.98 (m, 2H), 6.86 (d, J=8.0 Hz, 1H), 4.80 (m, 1H), 4.13 (m, 1H), 3.85 (s, 3H), 2.42 (br d, J=11 Hz, 1H), 2.13 (br t, J=13 Hz, 1H), 1.8 - 2.0 (m, 8H), 1.6 - 1.8 (m, 5H), 1.30 (dq, J=12, 4.5 Hz, 1H) ppm.

20

Example 2

Preparation of *cis*- and *trans*-[1-*tert*-butoxycarbonylamino-3-cyano-3-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexane]

Sodium cyanoborohydride (0.2 g, 3.2 mmol) was added to a mixture of 3-cyano-3-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexan-1-one (0.1 g, 0.32 mmol), ammonium
25 acetate (2.46 g, 31.9 mmol) and a spatula-tip of unactivated 3Å molecular sieves in methanol (35 mL) and the mixture was stirred for 65 h. The reaction was treated with 5% aqueous sodium carbonate, was extracted three times with 5:95 methanol/methylene chloride, was dried (K₂CO₃), was filtered and was concentrated. The crude mixture was
30 purified by flash chromatography, eluting with 5:95 methanol/methylene chloride, to afford an inseparable mixture of isomeric amines as a colorless oil (0.34 g, 34%). This mixture (0.34g, 1.0 mmol) was dissolved in methylene chloride (10 mL) and treated with di-*tert*-butyldicarbonate. After 16 h, the reaction was evaporated and the residue was purified by flash chromatography, eluting with 35:65 ether/hexanes, to provide two isomeric products:

35 a) *cis*-[1-*tert*-butoxycarbonylamino-3-cyano-3-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexane], a colorless oil, R_f 0.25 (35:65 ether/hexanes).

b) *trans*-[1-*tert*-butoxycarbonylamino-3-cyano-3-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexane], a colorless oil, R_f 0.15 (35:65 ether/hexanes).

Example 3

Preparation of *cis*-3-cyano-3-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexyl-1-amine, hydrochloride salt

- 5 A solution of *cis*-[1-*tert*.butoxycarbonylamino-3-cyano-3-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexane] (0.21 g, 0.52 mmol) in methylene chloride (2 mL) at 0°C under an argon atmosphere was treated with trifluoroacetic acid (0.5 mL, 6.5 mmol). After 2 h at room temperature, the reaction was neutralized with sodium bicarbonate, was extracted three times with 5:95 methanol/methylene chloride, was dried (K₂CO₃) and was
10 evaporated to obtain the free amine (0.18g, 97%) as a colorless oil. Treatment with hydrogen chloride-saturated ether provided the title compound as an off-white, very hygroscopic solid. mp 143-145°C. Anal. (C₁₉H₂₆N₂O₂·HCl·1.125 H₂O) calcd: C, 61.49; H, 7.94; N, 7.54; found: C, 61.47; H, 7.92; N, 7.23.

Example 4

Preparation of *trans*-[3-cyano-3-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexyl-1-amine, hydrochloride salt]

- Following the same procedure, except substituting *trans*-[3-cyano-3-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexyl-1-amine, hydrochloride salt], the title
20 compound was obtained as a pale gray, very hygroscopic solid. mp 187-188°C. Anal. (C₁₉H₂₆N₂O₂·HCl·0.5 H₂O) calcd: C, 63.41; H, 7.56; N, 7.78; found: C, 63.52; H, 7.93; N, 7.66.

Example 5

Preparation of *cis*-[1-acetamido-3-cyano-3-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexane]

- A solution of *cis*-[3-cyano-3-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexyl-1-amine] (0.15 g, 0.48 mmol), pyridine (0.135 mL, 1.67 mmol) and acetic anhydride (0.135 mL, 1.44 mmol) in dichloromethane (3 mL) was stirred at room temperature under an
30 argon atmosphere for 1 h. The solution was diluted with 5 % hydrochloric acid and was extracted twice with dichloromethane. The organic extracts were dried (magnesium sulfate) and evaporated. Purification by flash chromatography, eluting with 2:98 methanol/dichloromethane, provided *cis*-[1-acetamido-3-cyano-3-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexane] as a white foam. m.p. 52-54 °C. Anal. calcd.
35 (C₂₁H₂₈N₂O₃·0.25 H₂O): C 69.90; H, 8.00; N, 7.80; found: C, 69.93; H, 8.11; N, 7.49.

Example 6

Preparation of *trans*-[1-acetamido-3-cyano-3-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexane]

A solution of *trans*-[3-cyano-3-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexyl-1-amine] (0.15 g, 0.48 mmol), pyridine (0.135 mL, 1.67 mmol), and acetic anhydride (0.135 mL, 1.44 mmol) in dichloromethane (3 mL) was stirred at room temperature under an argon atmosphere for 3 h. The solution was diluted with 10% hydrochloric acid and extracted three times with dichloromethane. The organic extracts were dried (magnesium sulfate) and evaporated. Purification by flash chromatography, eluting with 2:98 methanol/dichloromethane, provided *trans*-[1-acetamido-3-cyano-3-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexane] as a white foam. m.p. 57-59°C. Anal. calcd. (C₂₁H₂₈N₂O₃·0.25 H₂O): C 69.90; H, 8.00; N, 7.80; found: C, 69.56; H, 8.15; N, 7.49.

Example 7

Preparation of *cis*-[N-*tert*.butoxycarbonyl-N-methyl-3-cyano-3-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexyl-1-amine]

To a suspension of sodium hydride, 60 % suspension in mineral oil (0.036 g, 0.90 mmol) and 15-crown-5 (2 drops) in dimethyl formamide (2 mL) at room temperature under an argon atmosphere was added a solution of *cis*-[1-*tert*.butoxycarbonylamino-3-cyano-3-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexane] (0.31 g, 0.75 mmol) in dimethyl formamide (2 mL) and the reaction was stirred 0.5 h. Methyl iodide (0.07 mL, 1.13 mmol) was added and stirring was continued an additional 0.5 h. The reaction was quenched with water and extracted twice with ethyl acetate. The combined extracts were washed four times with water and once with brine, was dried (magnesium sulfate) and evaporated. Purification by flash chromatography provided *cis*-[N-*tert*.butoxycarbonyl-N-methyl-3-cyano-3-(3-cyclopentyloxy-4-methoxyphenyl)-cyclohexyl-1-amine] as a white foam. m.p. 50-51°C.

Example 8

Preparation of *cis*-[N-methyl-3-cyano-3-(3-cyclopentyloxy-4-methoxyphenyl)-cyclohexyl-1-amine]

A solution of *cis*-[N-*tert*.butoxycarbonyl-N-methyl-3-cyano-3-(3-cyclopentyloxy-4-methoxyphenyl)-cyclohexyl-1-amine] (0.263 g, 0.61 mmol) and trifluoroacetic acid (1.0 mL, 13 mmol) in dichloromethane (5 mL) at room temperature under an argon atmosphere was stirred for 0.5 h. The reaction was diluted with sodium bicarbonate and water, was extracted with three times dichloromethane, was dried (magnesium sulfate) and was evaporated to provide *cis*-[N-methyl-3-cyano-3-(3-cyclopentyloxy-4-methoxyphenyl)-cyclohexyl-1-amine] as a colorless oil. ¹H-NMR (400 MHz, CDCl₃) δ 7.00 (m, 2H), 6.85

(m, 1H), 6.80 (s, impurity), 4.80 (m, 1H), 3.85 (s, 3H), 3.84 (s, impurity), 3.72 (m, impurity), 3.05 (s, 1H), 2.68 (m, 1H), 2.46 (s, 3H), 2.38 (m, 1H), 2.23 (m, 1H), 1.4 - 2.1 (m, 14H + impurity) ppm.

5

Example 9

Preparation of *cis*-[N-methyl-1-acetamido-3-cyano-3-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexane]

A solution of *cis*-[N-methyl-3-cyano-3-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexyl-1-amine] (0.10 g, 0.30 mmol), pyridine (0.12 mL, 1.50 mmol) and acetic anhydride (0.085 mL, 0.90 mmol) in dichloromethane (3 mL) was stirred at room temperature under an argon atmosphere for 1 h. The solution was washed with 10% hydrochloric acid, was dried (magnesium sulfate) and was evaporated. Purification by flash chromatography, eluting with 2:98 methanol/dichloromethane, provided *cis*-[N-methyl-1-acetamido-3-cyano-3-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexane] as a colorless oil. ¹H-NMR (400 MHz, CDCl₃) δ 6.81 (m, 2H), 6.77 (s, 1H), 4.77 (m, 1H), 3.82 (s, 3H), 3.74 (m, 1H), 2.93 (s, 3H), 2.72 (m, 1H), 2.42 (m, 1H), 1.8 - 2.0 (m, 9H), 1.72 (d, J=11Hz, 1H), 1.67 (s, 3H), 1.60 (m, 2H), 1.50 (m, 2H) ppm. Anal. calcd. (C₂₂H₃₀N₂O₃ · 0.9 H₂O) : C 68.33; H, 8.28; N, 7.24; found: C, 67.93; H, 7.86; N, 7.05.

20

Example 10

Preparation of *cis*-[N-methyl-N-methoxycarbonyl-3-cyano-3-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexyl-1-amine]

To a solution of *cis*-[N-methyl-3-cyano-3-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexyl-1-amine] (0.099 g, 0.30 mmol) and triethylamine (0.105 mL, 0.75 mmol) in tetrahydrofuran (1.5 mL) at 0°C under an argon atmosphere was added dropwise methyl chloroformate (0.025 mL, 0.33 mmol) and the resulting mixture was stirred for 0.5 h. The solution was quenched with water and was extracted three times with dichloromethane. The organic extracts were dried (magnesium sulfate) and evaporated. Purification by flash chromatography, eluting with 35:65 ethyl acetate/hexanes, provided *cis*-[N-methyl-N-methoxycarbonyl-3-cyano-3-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexyl-1-amine] as a colorless oil. ¹H-NMR (400 MHz, CDCl₃) δ 6.81 (s, 2H), 6.74 (s, 1H), 4.77 (m, 1H), 3.82 (s, 3H), 3.73 (m, 1H), 3.15 (s, 3H), 2.99 (s, 3H), 2.70 (m, 1H), 2.36 (m, 1H), 1.8 - 2.0 (m, 10H), 1.73 (d, J=11Hz, 1H), 1.4 - 1.6 (m, 3H) ppm. Anal. calcd. (C₂₂H₃₀N₂O₄ · 0.67 H₂O) : C 66.31; H, 7.92; N, 7.03; found: C, 66.31; H, 7.86; N, 6.78.

35

Example 11

Preparation of *trans*-[N-methoxycarbonyl-3-cyano-3-(3-cyclopentyloxy-4-

methoxyphenyl)cyclohexyl-1-amine]

To a solution of *trans*-[3-cyano-3-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexyl-1-amine] (0.152 g, 0.48 mmol) and triethylamine (0.17 mL, 1.20 mmol) in tetrahydrofuran (3 mL) at 0°C under an argon atmosphere was added dropwise methyl chloroformate (0.041 mL, 0.53 mmol) and the resulting mixture was stirred for 1.5 h. The solution was quenched with water and was extracted three times with dichloromethane. The organic extracts were dried (magnesium sulfate) and evaporated. Purification by flash chromatography, eluting with 3:7 ethyl acetate/hexanes, provided *trans*-[N-methoxycarbonyl-3-cyano-3-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexyl-1-amine] as a white foam. m.p. 49-51°C. Anal. calcd. (C₂₁H₂₈N₂O₄·0.25 H₂O): C 67.00; H, 7.70; N, 7.50; found C, 67.16; H, 7.82; N, 7.27.

Example 12Preparation of *cis*-[N-methoxycarbonyl-3-cyano-3-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexyl-1-amine]

To a solution of *cis*-[3-cyano-3-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexyl-1-amine] (0.247 g, 0.72 mmol) and dimethyl formamide (one drop, catalytic) in dichloromethane (3.5 mL) at 0°C under an argon atmosphere was added dropwise oxalyl chloride (0.70 mL, 0.79 mmol). The reaction was stirred for 1 h at room temperature, then was evaporated. The residue was dissolved in dry acetone (5 mL), cooled to 0°C, and added dropwise to a 0°C solution of sodium azide (0.162 g, 2.5 mmol) in water (0.75 mL). After 15 min, a mixture of hexanes (6 mL)/water (6 mL) was added and the mixture was twice more extracted with hexanes, was dried (magnesium sulfate), was diluted with toluene (5 mL), and the hexane was evaporated. After heating for 1 h at 80-85 °C, methanol (0.065 mL, 1.5 mmol) was added, and heating was continued for an additional hour, followed by room temperature stirring for 16 h and heating for 7 h. The reaction was diluted with water and was extracted three times with dichloromethane. The organic extracts were dried (magnesium sulfate) and evaporated. Purification by flash chromatography, eluting with 25:75 ethyl acetate/hexanes, provided *cis*-N-carboxymethyl-3-cyano-3-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexylamine (0.117 g, 44 %) as a white foam. m.p. 49-50 °C. Anal calcd (C₂₁H₂₈N₂O₄·0.125 H₂O): C, 67.31; H, 7.60; N, 7.48; found: C, 67.28; H, 7.53; N, 7.58.

METHODS OF TREATMENT

In order to use a compound of Formula (I) or a pharmaceutically acceptable salt thereof for the treatment of humans and other mammals, it is normally formulated in accordance with standard pharmaceutical practice as a pharmaceutical composition. The compounds of Formula (I) or a pharmaceutically acceptable salt thereof can be used in the

manufacture of a medicament for the prophylactic or therapeutic treatment of any disease state in a human or other mammal which is mediated by inhibition of PDE IV, such as but not limited to asthma, allergic, or inflammatory diseases. The compounds of Formula (I) are administered in an amount sufficient to treat such a disease in a human or other
5 mammal.

The method of treatment and monitoring for an HIV-infected human manifesting immune dysfunction or cytokine-mediated disease associated problems is taught in Hanna, WO 90/15534, December 27, 1990. In general, an initial treatment regimen can be copied from that known to be effective in interfering with TNF activity for other TNF mediated
10 disease states by the compounds of Formula (I). Treated individuals will be regularly checked for T cell numbers and T4/T8 ratios and/or measures of viremia such as levels of reverse transcriptase or viral proteins, and/or for progression of monokine-mediated disease associated problems such as cachexia or muscle degeneration. If no effect is seen following the normal treatment regimen, then the amount of the monokine activity
15 interfering agent administered is increased, e.g., by fifty percent per week.

The pharmaceutical composition of the present invention will comprise an effective, non-toxic amount of a compound of Formula (I) and a pharmaceutically acceptable carrier or diluent. The compounds of Formula (I) are administered in conventional dosage forms prepared by combining a compound of Formula (I) in an
20 amount sufficient to produce TNF production inhibiting activity, respectively, with standard pharmaceutical carriers according to conventional procedures. These procedures may involve mixing, granulating, and compressing or dissolving the ingredients as appropriate to the desired preparation.

Thus, if a solid carrier is used, the preparation can be tableted, placed in a hard
25 gelatin capsule in powder or pellet form, or in the form of a troche or lozenge. The amount of solid carrier will vary widely but preferably will be from about 25 mg to about 1 gram. When a liquid carrier is used, the preparation will be in the form of a syrup, emulsion, soft gelatin capsule, sterile injectable liquid such as an ampule or nonaqueous liquid suspension. Where the composition is in the form of a capsule, any routine
30 encapsulation is suitable, for example using the aforementioned carriers in a hard gelatin capsule shell. Where the composition is in the form of a soft gelatin shell capsule any pharmaceutical carrier routinely used for preparing dispersions or suspensions may be considered, for example aqueous gums, celluloses, silicates, or oils and are incorporated in a soft gelatin capsule shell. A syrup formulation will generally consist of a suspension or
35 solution of the compound or salt in a liquid carrier for example, ethanol, glycerine, or water with a flavoring or coloring agent.

The daily dosage regimen for oral administration is suitably about .001 mg/kg to 100mg/kg, preferably 0.01 mg/Kg to 40 mg/Kg, of a compound of Formula (I) or a

pharmaceutically acceptable salt thereof calculated as the free base. The active ingredient may be administered from 1 to 6 times a day, sufficient to exhibit activity.

While it is possible for an active ingredient to be administered neat, it is preferable to present it as a pharmaceutical formulation. The active ingredient may comprise, for
5 topical administration, from 0.001% to 10% w/w, e.g., from 1% to 2% by weight of formulation, although it may comprise as much as 10% w/w but preferably not in excess of 5% w/w and more preferably from 0.1% to 1% w/w of Formulation.

Formulations of the present invention comprise an active ingredient together with one or more acceptable carrier(s) thereof and optionally any other therapeutic
10 ingredient(s). The carrier(s) must be 'acceptable' in the sense of being compatible with the other ingredients of Formulation and not deleterious to the recipient thereof.

It will be recognized by one of skill in the art that the form and character of the pharmaceutically acceptable carrier or diluent is dictated by the amount of active ingredient with which it is to be combined, the route of administration, and other well-
15 known variables.

UTILITY EXAMPLES

EXAMPLE A

Inhibitory effect of compounds of Formula (I) on *in vitro* TNF production by human monocytes

20 The inhibitory effect of compounds of Formula (I) on *in vitro* TNF production by human monocytes may be determined by the protocol as described in Badger *et al.*, EPO published Application 0 411 754 A2, February 6, 1991, and in Hanna, WO 90/15534, December 27, 1990.

EXAMPLE B

25 Two models of endotoxic shock have been utilized to determine *in vivo* TNF activity for the compounds of Formula (I). The protocol used in these models is described in Badger *et al.*, EPO published Application 0 411 754 A2, February 6, 1991, and in Hanna, WO 90/15534, December 27, 1990.

The exemplified compounds herein demonstrated a positive *in vivo* response in
30 reducing serum levels of TNF induced by the injection of endotoxin.

No toxic effects are expected when these compounds are administered in accordance with the present invention.

EXAMPLE C

Isolation of PDE Isozymes

35 The phosphodiesterase inhibitory activity and selectivity of the compounds of Formula (I) can be determined using a battery of five distinct PDE isozymes. The tissues used as sources of the different isozymes are as follows: 1) PDE Ib, porcine aorta; 2) PDE Ic, guinea-pig heart; 3) PDE III, guinea-pig heart; 4) PDE IV, human monocyte; and 5)

PDE V (also called "Ia"), canine trachealis. PDEs Ia, Ib, Ic and III are partially purified using standard chromatographic techniques [Torphy and Cieslinski, Mol. Pharmacol., 37:206-214, 1990]. PDE IV is purified to kinetic homogeneity by the sequential use of anion-exchange followed by heparin-Sepharose chromatography [Torphy *et al.*, J. Biol. Chem., 267:1798-1804, 1992].

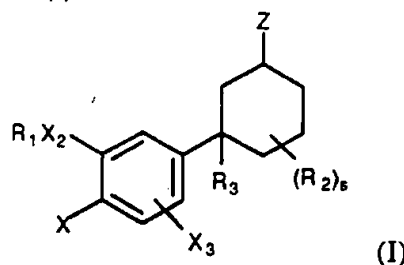
Phosphodiesterase activity is assayed as described in the protocol of Torphy and Cieslinski, Mol. Pharmacol., 37:206-214, 1990. Positive IC₅₀'s in the nanomolar to μ M range for compounds of the workings examples described herein for Formula (I) have been demonstrated.

EXAMPLE D

The ability of selected PDE IV inhibitors to increase cAMP accumulation in intact tissues is assessed using U-937 cells, a human monocyte cell line that has been shown to contain a large amount of PDE IV. To assess the activity of PDE IV inhibition in intact cells, nondifferentiated U-937 cells (approximately 10^5 cells/reaction tube) were incubated with various concentrations (0.01-1000 μ M) of PDE inhibitors for one minute and 1 μ M prostaglandin E₂ for an additional four minutes. Five minutes after initiating the reaction, cells were lysed by the addition of 17.5% perchloric acid, the pH was neutralized by the addition of 1M potassium carbonate and cAMP content was assessed by RIA. A general protocol for this assay is described in Brooker *et al.*, Radioimmunoassay of cyclic AMP and cyclic GMP., Adv. Cyclic Nucleotide Res., 10:1-33, 1979. The compounds of the working examples as described herein for Formula (I) have demonstrated a positive EC₅₀s in the μ M range in the above assay.

What is claimed is

1. A compound of Formula (I):



wherein:

- 5 R_1 is $-(CR_4R_5)_nC(O)O(CR_4R_5)_mR_6$, $-(CR_4R_5)_nC(O)NR_4(CR_4R_5)_mR_6$, $-(CR_4R_5)_nO(CR_4R_5)_mR_6$, or $-(CR_4R_5)_rR_6$ wherein the alkyl moieties may be optionally substituted with one or more halogens;

m is 0 to 2;

n is 1 to 4;

- 10 r is 0 to 6;

R_4 and R_5 are independently selected from hydrogen or a C_{1-2} alkyl;

- R_6 is hydrogen, methyl, hydroxyl, aryl, halo substituted aryl, aryloxy C_{1-3} alkyl, halo substituted aryloxy C_{1-3} alkyl, indanyl, indenyl, C_{7-11} polycycloalkyl, tetrahydrofuranyl, furanyl, tetrahydropyranyl, pyranal, tetrahydrothienyl, thienyl, 15 tetrahydrothiopyranyl, thiopyranyl, C_{3-6} cycloalkyl, or a C_{4-6} cycloalkyl containing one or two unsaturated bonds, wherein the cycloalkyl and heterocyclic moieties may be optionally substituted by 1 to 3 methyl groups or one ethyl group;

provided that:

- a) when R_6 is hydroxyl, then m is 2; or
 20 b) when R_6 is hydroxyl, then r is 2 to 6; or
 c) when R_6 is 2-tetrahydropyranyl, 2-tetrahydrothiopyranyl, 2-tetrahydrofuranyl, or 2-tetrahydrothienyl, then m is 1 or 2; or
 d) when R_6 is 2-tetrahydropyranyl, 2-tetrahydrothiopyranyl, 2-tetrahydrofuranyl, or 2-tetrahydrothienyl, then r is 1 to 6;

- 25 e) when n is 1 and m is 0, then R_6 is other than H in $-(CR_4R_5)_nO(CR_4R_5)_mR_6$; X is YR_2 , halogen, nitro, NR_4R_5 , or formyl amine;

Y is O or $S(O)_m$;

m' is a number having a value of 0, 1, or 2;

X_2 is O or NR_8 ;

- 30 X_3 is hydrogen or X;

R_2 is independently selected from $-CH_3$ or $-CH_2CH_3$ optionally substituted by 1 or more halogens;

s is 0 to 4;

R_3 is hydrogen, halogen, C_{1-4} alkyl, halo-substituted C_{1-4} alkyl,

CH₂NHC(O)C(O)NH₂, -CH=CR₈R₈', cyclopropyl optionally substituted by R₈', CN, OR₈, CH₂OR₈, NR₈R₁₀, CH₂NR₈R₁₀, C(Z')H, C(O)OR₈, C(O)NR₈R₁₀, or C≡CR₈;

Z' is O, NR₉, NOR₈, NCN, C(-CN)₂, CR₈CN, CR₈NO₂, CR₈C(O)OR₈, CR₈C(O)NR₈R₈, C(-CN)NO₂, C(-CN)C(O)OR₉, or C(-CN)C(O)NR₈R₈;

5 Z is OR₁₄, OR₁₅, SR₁₄, S(O)_mR₇, S(O)₂NR₁₀R₁₄, NR₁₀R₁₄, NR₁₄C(O)R₉, NR₁₀C(Y')R₁₄, NR₁₀C(O)OR₇, NR₁₀C(Y')NR₁₀R₁₄, NR₁₀S(O)₂NR₁₀R₁₄, NR₁₀C(NCN)NR₁₀R₁₄, NR₁₀S(O)₂R₇, NR₁₀C(CR₄NO₂)NR₁₀R₁₄, NR₁₀C(NCN)SR₉, NR₁₀C(CR₄NO₂)SR₉, NR₁₀C(NR₁₀)NR₁₀R₁₄, NR₁₀C(O)C(O)NR₁₀R₁₄, or NR₁₀C(O)C(O)OR₁₄;

10 Y' is O or S;

R₇ is -(CR₄R₅)_qR₁₂ or C₁₋₆ alkyl wherein the R₁₂ or C₁₋₆ alkyl group is optionally substituted one or more times by C₁₋₂ alkyl optionally substituted by one to three fluorines, -F, -Br, -Cl, -NO₂, -NR₁₀R₁₁, -C(O)R₈, -C(O)OR₈, -OR₈, -CN, -C(O)NR₁₀R₁₁, -OC(O)NR₁₀R₁₁, -OC(O)R₈, -NR₁₀C(O)NR₁₀R₁₁, -NR₁₀C(O)R₁₁,
15 -NR₁₀C(O)OR₉, -NR₁₀C(O)R₁₃, -C(NR₁₀)NR₁₀R₁₁, -C(NCN)NR₁₀R₁₁, -C(NCN)SR₉, -NR₁₀C(NCN)SR₉, -NR₁₀C(NCN)NR₁₀R₁₁, -NR₁₀S(O)₂R₉, -S(O)_mR₉, -NR₁₀C(O)C(O)NR₁₀R₁₁, -NR₁₀C(O)C(O)R₁₀, thiazolyl, imidazolyl, oxazolyl, pyrazolyl, triazolyl, or tetrazolyl;

q is 0, 1, or 2;

20 R₁₂ is C₃₋₇ cycloalkyl, (2-, 3- or 4-pyridyl), pyrimidyl, pyrazolyl, (1- or 2-imidazolyl), thiazolyl, triazolyl, pyrrolyl, piperazinyl, piperidyl, morpholinyl, furanyl, (2- or 3-thienyl), (4- or 5-thiazolyl), quinolinyl, naphthyl, or phenyl;

R₈ is independently selected from hydrogen or R₉;

R₈' is R₈ or fluorine;

25 R₉ is C₁₋₄ alkyl optionally substituted by one to three fluorines;

R₁₀ is OR₈ or R₁₁;

R₁₁ is hydrogen, or C₁₋₄ alkyl optionally substituted by one to three fluorines; or when R₁₀ and R₁₁ are as NR₁₀R₁₁ they may together with the nitrogen form a 5 to 7 membered ring optionally containing at least one additional heteroatom selected from O,

30 N, or S;

R₁₃ is oxazolidinyl, oxazolyl, thiazolyl, pyrazolyl, triazolyl, tetrazolyl, imidazolyl, imidazolidinyl, thiazolidinyl, isoxazolyl, oxadiazolyl, or thiadiazolyl, and each of these heterocyclic rings is connected through a carbon atom and each may be unsubstituted or substituted by one or two C₁₋₂ alkyl groups;

35 R₁₄ is hydrogen or R₇; or when R₁₀ and R₁₄ are as NR₁₀R₁₄ they may together with the nitrogen form a 5 to 7 membered ring optionally containing one or more additional heteroatoms selected from O, N, or S;

R₁₅ is C(O)R₁₄, C(O)NR₄R₁₄, S(O)₂R₇, or S(O)₂NR₄R₁₄;

provided that:

f) when X₂ is oxygen, X₃ and R₃ are hydrogen and s is 0, then R₃ is other than OH or OCH₃;

5 f) when Z is OH, X is YR₂ where Y is oxygen and R₂ is CH₃, X₂ is oxygen, X₃ is hydrogen, s is 0, and R₁ is CH₃, then R₃ is other than COOH;

g) when Z is OH, or OCH₃, X₂ is oxygen, X₃ is hydrogen, s is 0, and X is YR₂, then R₃ is other than H;

h) when Z is OS(O)₂C₁₋₆ alkyl or OS(O)₂ aryl, X₂ is oxygen, X₃ is hydrogen, s is 0, then R₃ is other than OR₈;

10 i) when R₁₂ is N-pyrazolyl, N-imidazolyl, N-triazolyl, N-pyrrolyl, N-piperazinyl, N-piperidinyl, or N-morpholinyl, then q is not 1; or

j). when Z is OH or OSO₂R₇ and R₃ is CH₃, CHOH or CH₂OC₁₋₃ alkyl, then R₁X₂ is not C₁₋₃ alkoxy and X is not halogen, methoxy, ethoxy, methylthio or ethylthio;

15 k) when Z is -NH₂, NH(C₁₋₃ alkyl), N(C₁₋₃ alkyl)₂, NH(CH₂)₂₋₅C(O)Ar where Ar is naphthyl or phenyl or Z is unsubstituted or substituted pyrrolidinyl, piperidinyl, morpholinyl or piperazinyl and R₃ is CH₃, CHOH or CH₂OC₁₋₃ alkyl, then R₁X₂ is not C₁₋₃ alkoxy and X is not halogen, methoxy, ethoxy, methylthio or ethylthio;

or a pharmaceutically acceptable salts thereof.

2. A compound of claim 1 which is:

20 *cis*-[N-methoxycarbonyl-3-cyano-3-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexyl-1-amine];

trans-[N-methoxycarbonyl-3-cyano-3-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexyl-1-amine];

25 *cis*-[N-methyl-N-methoxycarbonyl-3-cyano-3-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexyl-1-amine];

cis-[N-methyl-1-acetamido-3-cyano-3-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexane];

cis-[N-methyl-3-cyano-3-(3-cyclopentyloxy-4-methoxyphenyl)-cyclohexyl-1-amine];

30 *cis*-[N-*tert*-butoxycarbonyl-N-methyl-3-cyano-3-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexyl-1-amine];

trans-[1-acetamido-3-cyano-3-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexane];

cis-[1-acetamido-3-cyano-3-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexane];

trans-[3-cyano-3-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexyl-1-amine,

35 hydrochloride salt];

cis-3-cyano-3-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexyl-1-amine, hydrochloride salt];

cis-[1-*tert*-butoxycarbonylamino-3-cyano-3-(3-cyclopentyloxy-4-

methoxyphenyl)cyclohexane]

b) *trans*-[1-*tert*.butoxycarbonylamino-3-cyano-3-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexane]; and

cis- and *trans*-[3-cyano-3-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexan-1-ol].

5 3.A pharmaceutical composition comprising a compound of Formula (I) according to claim 1 and a pharmaceutically acceptable excipient.

10 4.A method for treating an allergic or inflammatory state which method comprises administering to a subject in need thereof an effective amount of a compound of Formula (I) according to claim 1 alone or in combination with a pharmaceutically acceptable excipient.

5.A method for inhibiting the production of tumor necrosis factor which comprises administering to a subject in need thereof an effective amount of a compound of Formula (I) according to claim 1 alone or in combination with a pharmaceutically acceptable excipient.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US94/10798

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) : A61K 31/375; C07C 255/46

US CL : 514/520; 558/426

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/520; 558/426

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
CAS ONLINE**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	Chemical Abstracts, Vol 115, issued 1991, Solomina et al, "Synthesis of 6,7-dimethoxy-2-methyl-4,4'-spiro-1'-(3-amino-2-hydroxypropoxy)cyclohexane-1,2,3,4-tetrahydroisoquinolines and their biological activity," see abstract no. 8542s.	1-4
T	Chemical Abstracts, vol. 120, issued 1994, Christensen et al, "Cyclohexylbenzones useful for treating allergic or inflammatory diseases," see abstract no. 191326q.	1-4

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:	*T	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
A document defining the general state of the art which is not considered to be of particular relevance	*X*	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
E earlier document published on or after the international filing date	*Y*	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	*Z*	document member of the same patent family
O document referring to an oral disclosure, use, exhibition or other means		
P document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search

18 JANUARY 1995

Date of mailing of the international search report

31 JAN 1995

Name and mailing address of the ISA/US
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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US94/10798

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☒ Claims Nos.: 1, 3-5
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

Please See Extra Sheet.
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐

The additional search fees were accompanied by the applicant's protest.

☐

No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US94/10798

BOX 1. OBSERVATIONS WHERE CLAIMS WERE FOUND UNSEARCHABLE

2. Where no meaningful search could be carried out, specifically:

Aside from the specific non-heterocyclic cyano structures of page 12 lines 13-35 (same compounds as Examples 1-12 and claim 2), compounds with clearly defined structures, the terms used in the unsearchable claims cannot be ascertained into meaningful enough specific compound structures such as to afford a determination of proper specific subclasses to search. Thus, the unsearchable claims will be searched only to the extent they read on searchable features (the above compounds) in the description and claims.